Claims

1. A crystallised molecular complex of an E2 N-terminal module (E2NT) dimer protein or homologue thereof, comprising residues vital for transcriptional and replicational activities of said protein.

2. An E2NT dimer protein according to Claim 1 wherein the residues lie on opposite sides of an N-terminal domain.

3. An E2NT dimer protein according to either preceding claim wherein the residues comprise a plurality of residue clusters associated with a structural role at an interface between N1 and N2 terminal domains of respective monomers within the dimer.

4. An E2NT dimer according to Claim 3 comprising three clusters.

5. An E2NT dimer according to either of Claims 3 or 4 wherein a first cluster of vital residues is associated with interactions between N1 and N2 domains and comprises any one or more of the following residues Ile82, Glu90, Trp92, Lys112, Tyr138, Val145.

6. An E2NT dimer according to any one of Claims 3-5 wherein a second cluster of residues is associated with N1 interactions and comprises either or both of residues Trp33 and Leu94.

7. An E2NT dimer according to any one of Claims 3-6 wherein a third cluster of residues is associated with N2 interactions and comprises any one or more of the following residues Pro106, Lys111, Phe168, Trp134.

8. An E2NT dimer according to any preceding claim further comprising residues associated with transactivation and/or replication properties of E2.

9. An E2NT dimer according to Claim 8 wherein the residues comprise any one or more of the following residues Glu20, Glu100, Asp122, Arg37, Glu39, Ile73, Gln12 and Ala69.

10. Use of a crystallised molecular complex of an E2 N-terminal module (E2NT) dimer protein according to any preceding claim or homologue thereof in mapping mutations onto an E2 three-dimensional structure so as to identify areas of amino acid conservation and the effect of mutations on folding of the E2 protein.

11. Use according to Claim 10 in rationalised antiviral drug design.

12. An *in vitro* method for identifying and/or selecting a candidate therapeutic agent, the method comprising determining interaction of a E2 N-terminal module (E2NT) dimer in a sample by contacting said sample with said candidate therapeutic agent and measuring DNA loop formation in E2.

13. Use of the method according to Claim 12 in identifying and/or selecting an antiviral candidate therapeutic agent.

14. Use according to Claim 13 wherein identification/selection of the candidate therapeutic agent depends on its ability to interfere with or block interactions of E2NT so as to interfere or block viral and/or cellular transcription factors.

15. Use of an E2NT dimerisation inhibitor for the preparation of a medicament for treatment of conditions that arise as a result of HPV infection.

16. Use according to Claim 15 for the treatment of warts, proliferative skin lesions and/or cervical cancer.

17. A method of monitoring the efficacy of an antiviral therapy in a patient receiving a medicament for the treatment of an HPV infection comprising taking a sample from said patient and measuring E2NT interactions and/or DNA loop formation.

18. Use of a dimerisation surface of an crystallised molecular complex of an E2 N-terminal module (E2NT) dimer protein or homologue thereof according to any one of Claims 1-9 as a target site for interaction with putative antiviral agents and/or for measuring efficacy of said agents.

19. A method for identifying and/or selecting a candidate therapeutic agent, comprising applying rationalised drug design to a crystal structure obtainable by crystallising E2NT, cryogenically freezing the crystals and generating the crystal structure using X-ray diffraction.

20. A method of claim 19, wherein the method by which the E2NT crystal structure is obtainable comprises crystallisation using hanging-drop vapour diffusion.

21. A method of claim 19 or claim 20 wherein the method by which E2NT crystal structure is obtainable comprises X-ray diffraction using uranium acetate and gold cyanide E2NT derivatives and refining with data extending to 1.9 Å spacing.

22. A method of any of claims 19 to 21, wherein the crystal structure comprises the portions of amino acids Ile82, Glu90, Trp92, Lys112, Tyr138, Val145, Pro106, Lys111, Phe168, Trp134, Trp33 and Leu94.

23. A method of any of claims 19 to 22, wherein the rationalised drug design comprises designing drugs which interact with the dimerisation surface of E2NT.

24. A computer for producing a three-dimensional representation of a molecule or molecular complex, wherein said molecule or molecular complex comprises or a

three-dimensional representation of a homologue of said molecule or molecular complex, wherein said homologue comprises a binding pocket that has a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5Å, wherein said computer comprises:

(a) a machine-readable data storage medium comprising a data storage material encoded with machine-readable data, wherein said data comprises the structure coordinates of E2NT amino acids Ile82, Glu90, Trp92, Lys112, Tyr138, Val145, Pro106, Lys111, Phe168, Trp134, Trp33 and Leu94 according to Table 3;

(b) a working memory for storing instructions for processing said machine-readable data;

(c) a central-processing unit coupled to said working memory and to said machine-readable data storage medium for processing said machine readable data into said three-dimensional representation; and

(d) a display coupled to said central-processing unit for displaying said three-dimensional representation.

25. The computer according to claim 24, wherein said three-dimensional representation is of a molecule or molecular complex is defined by the set of structure coordinates according to Table 3, or wherein said three-dimensional representation is of a homologue of said molecule or molecular complex, said homologue having a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5 Å.

26. A computer for determining at least a portion of the structure coordinates corresponding to an X-ray diffraction pattern of a molecule or molecular complex, wherein said computer comprises:

(a) a machine-readable data storage medium comprising a data storage material encoded with machine-readable data, wherein said data comprises at least a portion of the structural coordinates according to Table 3;

(b) a machine-readable data storage medium comprising a data storage material encoded with machine-readable data, wherein said data comprises an X-ray diffraction pattern of said molecule or molecular complex;

(c) a working memory for storing instructions for processing said machine-readable data of (a) and (b);

(d) a central-processing unit coupled to said working memory and to said machine-readable data storage medium of (a) and (b) for performing a Fourier transform of the machine readable data of (a) and for processing said machine readable data of (b) into structure coordinates; and

(e) a display coupled to said central-processing unit for displaying said structure coordinates of said molecule or molecular complex.

27. A crystallised molecule or molecular complex comprising a dimerisation surface defined by structure coordinates of E2NT amino acids Ile82, Glu90, Trp92, Lys112, Tyr138, Val145, Pro106, Lys111, Phe168, Trp134, Trp33 and Leu94 according to Table 3or a homologue of said molecule or molecular complex, wherein said homologue comprises a binding pocket that has a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5Å.

28. The crystallized molecule or molecular complex according to claim 27, wherein said molecule or molecular complex is defined by the set of structure coordinates according to Table 3, or a homologue thereof, wherein said homologue has a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5Å.

29. A machine-readable data storage medium, comprising a data storage material encoded with machine readable data which, when using a machine programmed with instructions for using said data, is capable of displaying a graphical three-dimensional representation of a molecule or molecular complex comprising a dimerisation surface defined by structure coordinates of E2NT amino acids Ile82, Glu90, Trp92, Lys112, Tyr138, Val145, Pro106, Lys111, Phe168, Trp134, Trp33 and Leu94 according to Table 3, or a homologue of said molecule or molecular complex, wherein said homologue comprises a binding pocket that has a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5Å.

30. The machine-readable data storage medium according to claim 7, wherein said molecule or molecular complex is defined by the set of structure coordinates according to Table 3, or a homologue of said molecule or molecular complex, said homologue having a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5Å.

31. A machine-readable data storage medium comprising a data storage material encoded with a first set of machine readable data which, when combined with a second set of machine readable data, using a machine programmed with instructions for using said first set of data and said second set of data, can determine at least a portion of the structure coordinates corresponding to the second set of machine readable data, wherein: said first set of data comprises a Fourier transform of at least a portion of the structural coordinates according to Table 3; and said second set of data comprises an x-ray diffraction pattern of a molecule or molecular complex.

32. A method for evaluating the ability of a chemical entity to associate with a molecule or molecular complex according to claim 27 or claim 28 comprising the steps of:

a. employing computational means to perform a fitting operation between the chemical entity and a dimerisation surface of the molecule or molecular complex; and

b. analysing the results of said fitting operation to quantify the association between the chemical entity and the dimerisation surface.

33. A drug or therapeutic agent identified, assessed or selected using a crystallised molecular complex of an E2NT protein or its crystal structure or using a complex of any of claims 1 to 9, a method of claim 12, a use of any of claims 13, claim 14 or 18. a method of any of claims 20 to24 or 32 or a product of any of claims 25 to 31.